



Case Report

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Vagaries of the Host Response to Chronic Hepatitis B Virus Infection: What is the Ultimate Outcome of So-called "Asymptomatic HBV Carriers" Observed Over Several Decades?

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ABSTRACT

Introduction: Chronic hepatitis B virus (HBV) infection is prevalent worldwide and up to 40% is known to progress to serious complications including cirrhosis and hepatocellular carcinoma (HCC). The outcome of the remaining infected individuals is not well documented. Our case series describes a longer cohort of chronic HBV infections that have remained asymptomatic with no progression of liver disease.

Case Series: Thirty-three patients (ages 31-84) with chronic HBV infection were identified. All patients had no significant elevations in transaminase levels and were followed over 32 years, collectively. 18/33 had a fluctuating greater magnitude of HBV viral load with no elevations in tumor marker or significant radiographic changes to their liver.

Discussion/Conclusion: Chronic HBV infection can lead to serious complications over time, the mechanism of which are not well understood. The variation in patients that do and do not develop these complications stresses the importance of the individual response to the virus and may highlight host immune response differences.

Introduction

Since the discovery of hepatitis B virus (HBV) by Blumberg et al. in 1965, his first vaccine in 1982, and subsequently highly effective antiviral drugs, there has been a significant decrease in the number of infected people globally and especially in younger generations.¹ However, it is critical to study chronic HBV infection as it is still responsible for nearly 50% of hepatocellular carcinoma (HCC) worldwide and 600,000 to one million die annually from HBV-related liver disease.²⁻⁶

Fifteen to 40% of patients with chronic HBV are expected to progress to cirrhosis and HCC.^{7,8} Previous studies have observed the outcomes of the remaining individuals who do not develop these complications. However, the longest follow up is 10-18 years.⁹⁻¹⁵ In contrast, our case series presents 33 patients followed over a maximum of 32 years, some of which have been HBV carriers since birth and are in their 80s.

Hepatitis B virus is a DNA virus that spreads from blood and bodily fluids of an infected host.¹⁶ After transmission, the natural history of the viral infection depends on the initial host immune response: does the immune system successfully clear the virus after initial attack, or does it struggle to do so and commit to a life-long

battle between host and virus? If the latter occurs, the patient is said to have chronic HBV infection.¹⁶

The diagnosis of HBV infection can be broken into subtypes, the nomenclature of which has evolved over time but is based on the activity of the virus (measured by HBV DNA, hepatitis B e-antigen (HBeAg), and the response from host (ALT levels, anti-HBe and anti-HBs).¹⁶

At first, before the immune system embarks a response, ALT levels are low while viral DNA level is high (immune tolerant or HBeAg positive chronic HBV infection).¹⁶ The immune system eventually fights back, causing elevations in ALT as the HBV infected hepatocytes are destroyed (immune reactive, or HBeAg positive, chronic hepatitis B).¹⁶ This eventually leads to low levels of HBV DNA and ALT, as the immune system keeps the virus at bay (inactive carrier or HBeAg negative, chronic HBV infection) and might even lead to clearance of the virus by CD8 and CD4 cell activities.^{16,17} If it is not totally cleared, at times, the virus DNA levels can intermittently rise but not to a degree to cause much change in ALT (HBeAg negative chronic hepatitis).¹⁶ During all of these stages, HBsAg remains positive, as the virus is always replicating regardless of the rate or degree of response it has from the immune system. The last stage, considered resolution of the infection, occurs when HBsAg disappears (1-3%).¹⁸ However, most patients do not reach this stage and remain infected for many years, during which complications can ensue such as hepatocellular carcinoma (HCC) or cirrhosis.

Considering the struggle between the host immune system and the virus described above, an inverse correlation has been observed between chronicity of HBV infection and the age at the time of exposure to the virus. The risk of developing chronic HBV infection depends on the age of exposure to HBV: 90 to 100% probability if exposed to HBeAg (+) mothers during birth (perinatal infection), 25 to 30% probability during infancy and childhood under 5 years, and less than 5% in adults.¹⁹⁻²³ Moreover, most of the neonatal and perinatal HBV infections become persistent and up to 40% of chronically infected HBV individuals eventually develop cirrhosis or HCC.⁹ The outcome of the remaining who do not develop these complications is not well known or described except for small random reports.

Some reports have described two forms of HBsAg positive, HBeAg negative subjects with normal ALT levels: those who are true healthy carriers and others with chronic HBV infection with transient virological and biochemical remission.^{9,24}

Our purpose of this 33-case series is to display and examine longitudinally collected data from patients with asymptomatic, inactive chronic HBV infections that have not undergone treatment or developed HCC or cirrhosis. As described by Puoti in 2013, we have also observed two groups of patients: both of which had low ALT levels but one group with fluctuating HBV DNA levels and the other with consistently low DNA levels.⁹ Both groups did not require antiviral therapy and have not developed cirrhosis or HCC up to 32 years of collective follow up.

Case Series

Thirty-three patients were identified for this case series. Median current age is 54.6 (range 31-84 years old) with the follow up period between 1989 and 2021. Patients, on average, were infected for 26.35 years and were followed for 7.45 years at our institution. Many were also infected at birth. All patients were HBeAg (-) by the time of first follow up. 32/33 were Asian American and one was African American. No patients in this case series had significant comorbidities, including: metabolic disease, alcohol or drug use disorder, genetic disorders affecting the liver, or immunosuppressive disorders. Further, none were using immunosuppressive medications that could have contributed to host response to virus.

Table 1 shows 33 cases (follow up ranging 1989-2021, average of 7.45 years) organized into two broad categories with corresponding transmission and age: those with low ALT levels and persistently low levels of HBV DNA longitudinally, and those with low ALT levels and fluctuating higher levels of HBV DNA with closer follow up and monitoring. Fluctuating higher levels of DNA were defined by ranges that included values greater than 1,000 IU/mL. Many also had median values greater than 1,000 IU/mL. Patients were organized into these two groups to better display the varying presentation of chronic hepatitis B infection patterns over time. Tables 2 and 3 further characterize these two broad groups, displaying biochemical data and trends. All patients are HBeAg (-) and have maintained normal ALTs throughout the observation period.

Patients that had fluctuating HBV DNA levels had closer follow up which, in addition to hepatic function, CBC, and renal function, included regular liver imaging and AFP monitoring. As displayed in table 4, in addition to low to normal ALT levels, low AFP and normal imaging rationalized continued regular monitoring these patients without initiation of antiviral treatment.

Table 1: Two major groups of patients with their respective family history and median age

Patterns of laboratory values	Total	Transmission			Median Age
		Maternal	Paternal	Unknown	
Both low ALT and low HBV DNA	15	10	1	4	61 (36-84)
Low-normal ALT and fluctuating HBV DNA	18	7	3	8	51 (31-71)

Table 2: Patients with persistently low ALT and low HBV DNA levels, their years of HBV infection, and associated characteristics

Case	Age/Sex	Years with known HBsAg+ status	Follow up date range	No. of follow ups	Median HBV DNA IU/ml	HBV DNA IU/ml Ranges	Transmission M (maternal) P (paternal) U (unknown)
1	80/F	80	6/2017- 1/2019	4	40	0-60	M
3	62/M	62	1/2011- 7/2019	7	20	0-26	M
5	72/F	53	7/2015- 3/2021	15	63	20-237	U
6	54/F	22	8/2019- 8/2020	2	<10	<10	U
7	84/F	84	5/1989- 8/2021	9	221	5-436	M
11	47/F	47	2/2008-10/2020	7	69	19-619	M
14	62/F	62	10/2011-6/2021	19	155	30-549	M
15	62/M	62	3/2014- 8/2021	10	70	9-120	M
17	36/F	36	4/2008- 8/2021	13	30	19-140	M
18	50/F	50	9/2018- 4/2021	6	10	9-240	M
21	63/F	63	11/2015-6/2021	17	23	19-242	M
24	44/F	44	8/2012- 10/2016	5	20	20-120	M
25	35/M	19	8/2016- 10/2018	6	90	10-320	P
32	61/M	23	7/2020-7/2021	2	65	31-99	U
33	69/M	20	1/2008-8/2021	12	141	30-895	U

Table 3: Patients with low ALT and fluctuating higher HBV DNA levels, their years of HBV infection, and associated characteristics

Case	Age/Sex	Years with known HBsAg+ Status	Follow up date range	No. of follow ups	Median HBV DNA IU/ml	HBV DNA IU/ml ranges	Transmission M (maternal) P (paternal) U (unknown)
2	56/M	34	10/2016-7/2021	19	700	0-2,050	U
4	43/F	28	10/2008-6/2021	21	3,100	638-10,000	U
8	55/M	33	1/2009-10/2019	12	165	9-1,431	P
9	71/F	30	1/2017-3/2021	8	550	159-1,880	U
10	68/M	38	10/2011-4/2021	13	604	110-3,400	U
12	55/F	55	10/2002-4/2021	32	2,185	90-1,900,000	M
13	52/F	52	12/2016-10/2021	13	1,091	417-4,000	M
16	45/F	45	11/2010-2/2019	7	2,353	1,100-3,333	M
19	40/F	30	12/2018-3/2021	6	855	820-1,000	M
20	57/F	57	5/2013-12/2020	12	2,240	230-5,890	M
22	56/M	36	12/2017-7/2021	9	230	30-1,751	P
23	50/M	50	6/2014-11/2019	10	14,000	1,300-40,000	M
26	31/F	31	4/2014-2/2021	16	585	30-1,500	M
27	41/F	7	11/2016-6/2021	5	1,270	410-5,140	P
28	63/M	13	1/2018-6/2021	5	140,000	42,500-511,000	U
29	34/M	6	8/2015-7/2021	6	1,075	200-5,735	U
30	45/M	5	1/2016-3/2020	4	10,585	6,180-116,000	U
31	41/F	7	11/2014-5/2021	8	6,570	3,590-28,700	U

Tables 5 and 6 display details of the family history for those with maternal and paternal transmission, respectively. Many had family members with serious complications (HCC, cirrhosis), while the patients under study have maintained many years of asymptomatic status.

Overall, 17 out of 33 patients had maternal transmission (17/33, 52%), with supposed years of infection ranging 31 to 84 years. Four patients were infected through paternal transmission and 12 from an unknown route. The average length of follow up after diagnosis for all patients was

26.35 years, though the years with known HBsAg status for paternal transmission and unknown groups are a rough estimate of the length of their hepatitis B infection. For those infected at birth, the infected duration is their age.

Discussion

This case series presents 33 patients with chronic, asymptomatic HBV infection that remained in a mostly inactive state for many years without developing known complications such as HCC or cirrhosis. The majority of patients with known maternal or paternal transmission

Table 4. ALT and AFP levels for patients with normal ALT and fluctuant HBV DNA levels

Case	Age/Sex	Yrs with HBsAg (+) status	No. Tested	Average ALT IU/ml (range)	Median AFP ng/ml (ranges)	Median Creatinine mg/dL (ranges)	Imaging/ Ultrasound
2	56/M	34	19	48 (36-61)	2.8 (2.1-3.2)	0.8 (0.69-0.92)	Fatty infiltration
4	43/F	28	21	13 (9-26)	2.9 (1.4-3.9)	0.69 (0.58-0.82)	Normal
8	55/M	33	12	12 (7-15)	2.5 (1.9-4.1)	0.84 (0.8-1.02)	Normal
9	71/F	30	8	23 (19-35)	3.4 (3.1-3.7)	0.57 (0.53-0.63)	Normal
10	68/M	38	13	19(15-23)	2.6 (1.8-2.9)	0.8 (0.73-0.96)	Increased echogenicity
12	55/F	55	32	21 (12-54)	10.5 (0.6-2.0)	0.6 (0.46-0.7)	Mild increased echogenicity
13	52/F	52	13	16 (13-23)	2.9 (2.7-3.3)	0.64 (0.58-0.76)	n/a
16	45/F	45	7	12 (9-13)	2.7 (2.2-5.1)	0.68 (0.62-0.74)	Normal
19	40/F	30	6	16 (13-21)	1.4 (1.2-2.1)	0.63 (0.56-0.76)	Normal
20	57/F	57	12	25 (15-31)	2.5	0.65 (0.6-0.7)	Normal
22	56/M	36	9	28 (23-32)	3.0 (2.5-3.6)	0.86 (0.79-0.92)	Mild increased echogenicity
23	50/F	50	10	16 (10-30)	2.8 (0.65-3.4)	0.67 (0.61-3.6)	Normal
26	31/F	31	16	21 (16-34)	2.5 (1.8-2.7)	0.69 (0.63-0.84)	Normal
27	41/F	7	5	14 (12-15)	3.5 (3.4-3.6)	0.66 (0.63-0.66)	Normal
28	63/M	13	5	36 (29-43)	3.35 (2.9-3.8)	0.86 (0.8-0.99)	Normal
29	34/M	6	6	43 (31-66)	3.9 (3.6-5.2)	0.99 (0.96-1.13)	Normal
30	45/M	5	4	21 (19-24)	2.6	0.59 (0.58-0.6)	Mildly coarsened echotexture
31	41/F	7	8	17 (13-19)	6 (4.9-6.4)	0.8 (0.63-0.84)	Normal

Table 5: Highlighted family history of those with maternal HBV transmission

Patient	Age/Sex	Family history maternal side	Family history on siblings and children
1	80/F	Mother died of HCC at age 86	Three brothers that are positive Four children are positive
3	62/M	Mother is 87 years old with Anti-HBs	Brother died of HCC at age 41. Three sisters and another older brother are positive
7	84/F	Mother died of hypertension at age 59	Son died of HCC at age 44 Brother had bad liver disease
11	47/F	Mother positive	Sister positive
12	55/F	Mother positive	Sister positive
13	52/F	Maternal grandmother died of HCC. Mother with liver disease	Three siblings positive
14	62/F	Mother died of CVA	8 siblings positive. One brother died of cirrhosis
15	62/M	Mother died of cirrhosis at age 39	n/a
16	45/F	Mother with chronic Hep B, one maternal uncle with HCC cirrhosis waiting for transplant, two maternal aunts positive. Maternal grandfather died of cirrhosis	n/a
17	36/F	Mother with chronic hep b	Sister is positive
18	50/F	Mother positive	Brother positive
19	40/F	Mother with chronic hep b	n/a
20	57/F	n/a	Brother with chronic HBV infection
21	63/F	n/a	Brother HBV carrier
24	44/F	Mother positive	Two brothers positive
26	31/F	Maternal grandmother with cirrhosis, liver transplant. Three maternal aunts with HBV infection	Older brother HBsAg (+)

Table 6: Highlighted family history of those with paternal HBV transmission.

Patient	Age/Sex	Family history paternal side	Family history on siblings and children
8	55/M	Father and paternal uncle positive	n/a
22	56/M	Father died of HCC at age 50	Brother positive
25	35/M	Father and paternal uncle positive	n/a
27	42/F	Strong family history of HBV on father's side	Brother positive

also had family histories of liver-related morbidity and mortality. This raises the question of what leads to hepatocarcinogenesis in some and not others and can be partially answered by examining the details in this case series. Further, the two major groups identified from these cases were those with low ALT and HBV DNA levels versus those with low ALT but fluctuating HBV DNA levels. Both have had similar outcomes but display, through biochemical data, the differences among virus-host response.

Patient Characteristics

The patients' characteristics provide insight into the pathogenesis and epidemiology of HBV, which may have implications on complications related to the infection. Although some cases had an unknown means of transmission, most contracted HBV infection at birth or at a young age through a maternal or paternal source (20 out of 33). This highlights previous findings that patients infected with HBV at a young age likely progress to chronic HBV infection as their immune systems are not mature enough to clear the virus.²⁵ It has been shown that those that fail to clear the virus after first insult and thus develop chronic hepatitis B have a weak T-cell specific response to the virus.²⁶ Nearly all of the identified patients are also of Asian descent, which speaks to the epidemiology of HBV and world populations most at risk of the disease.¹⁶ Further, our patients may also share similar genotypes of the virus, as studies have shown a correlation between geographic distribution and HBV genotype.^{16,25}

Host Variability and Hepatocarcinogenesis of Hepatitis B Virus

Many cases in this series display a common theme: maternal or paternal transmission with a family history of HCC or cirrhosis. It can be assumed that the patients have a similar if not identical genotype that their family members had yet have not developed similar complications even at a median advanced age of 54.6 years old. Assuming that other factors that contribute to liver inflammation such as environmental, metabolic, and toxin-induced (alcohol, etc) did not exist within these families, the variability in clinical outcomes may highlight the variations within the host itself. Other studies have commented on a variable host response to the virus including factors that may play a role such as gender and stress.²⁷⁻²⁹ It is clear that the immune system plays a vital role in the pathogenesis of chronic hepatitis B and thus may also contribute to the variability of clinical outcomes in these cases as well.^{26,28} Further, the pattern of lab data for our two main groups (low ALT and HBV DNA, low ALT with fluctuating HBV DNA) also display the "struggle" between host immune system and viral replication over time.

The pathogenesis of HBV associated HCC is not fully understood. One of the proposed theories involved virus

integration into host DNA.³⁰ Studies have found that even in the phases of chronic HBV infection where ALT levels are normal (like in the immune tolerant phase), the virus is integrating itself into the host's DNA, which may in turn lead to cellular dysregulation and carcinogenesis.³⁰ This is also supported by studies that have found the presenting magnitude of viremia to be linked to future risk of HCC.³¹ Interestingly, the patients in this series have presumably had many years of host DNA-virus genome integration but have not developed HCC. Therefore, the length of inactive CHB status might not be a strong risk factor. This contrasts the theory that all hepatocarcinogenesis is driven by the immune system response as witnessed by elevations in ALT.

Case 12 (table 3) highlights a patient with periods of increased viral replication as displayed by the wide range of viral DNA over the course of 17 years of follow up. However, they never displayed elevations in ALT or had imaging findings or laboratory evidence (in the form of AFP elevations) to suggest cancerous growth. Not only might this suggest that the host's immune system did not lead to a strong enough inflammatory response to cause ALT elevations, but also suggests that having significant peaks in viral load over the years is not always enough to lead to carcinogenesis. Other patient cases including 4, 16, 20, 23, 28, and 31 had median values >2,000 IU/mL, above which has been cited as an increased risk of developing complications.⁹ Contrastingly, many other cases had persistently lower levels of viral DNA and also did not develop complications. Thus, this case series supports the theories that immune response significant enough to raise ALT levels may be a more clinically relevant risk factor for the development of HCC. It also highlights the varied host response to virus: fluctuating DNA levels displays a response from the immune system, but not one great enough to cause elevations in ALT or complications such as cirrhosis or HCC.

Strengths and Limitations

Compared to other similar studies that have collected data longitudinally on patients with chronic HBV infection, this series has the longest time frame of patient follow-up.^{11,32,33} Limitations include those common to case series and case reports, including low sample size, lack of a control group and retrospective analysis with missing or incomplete data. In particular, our sample size is low in comparison to the large number of Hepatitis B virus infections worldwide, and thus cannot serve as an overall trend of disease pattern.

Summary and Conclusions

This case series presents data from 33 patients with asymptomatic chronic HBV infection, ranging from current age 31-84, over a maximum of 32 years (1989-2021).

No patients have developed HCC or cirrhosis, including those with strong family histories of these complications and those with great magnitude and fluctuating levels of viremia. There were two main groups of patients: those with both low ALT levels and low HBV DNA versus those with low ALT but higher fluctuating HBV DNA levels, both of which have had similar clinical outcomes but display the varieties in host response to virus. These findings suggest that there may be more to elucidate within the host to better understand what patients are at risk for developing complications and, in particular, HCC. Findings may support that a more robust immune response to the virus that leads to elevations in ALT may be a stronger risk factor than the length or magnitude of viremia.

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